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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/041,018	01/07/2002	Seiichi P.T. Matsuda	HO-P02080US1	2605

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EXAMINER	
RAMIREZ, DELIA M	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 09/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/041,018	MATSUDA ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-18,29,32,80-115,117-120,122-129 and 132-134* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,4-18,80,98,99,102-106,112-115,122-125,132 and 133* is/are allowed.

6)☒ Claim(s) *29,32,81-97,100,101,107-111,117-120,126-129 and 134* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/21/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 1, 4-18, 29, 32, 80-115, 117-120, 122-129 and 132-134 are pending.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 6/21/2006 has been entered.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on 6/21/2006 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Objections

2. Claim 29 is objected to due to the recitation of "polypeptide having an amino acid sequence of SEQ ID NO: 22 of a geranylgeranyl pyrophosphate synthase" and "polypeptide having an amino acid sequence of SEQ ID NO: 383 of a diterpene synthase". While the Examiner has interpreted the terms as encompassing polypeptides having geranylgeranyl pyrophosphate synthase activity and diterpene synthase activity, respectively, it is suggested that for clarity and consistency with commonly used claim language, the terms be amended to recite "geranylgeranyl pyrophosphate synthase having.....sequence of

SEQ ID NO: 22" and "diterpene synthase having ...sequence of SEQ ID NO: 383", or similar.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 29, 32, 81-97, 100-101, 107-111, 117-120, 126-129, 134 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As stated in MPEP 2111.01, during examination, the claims must be interpreted as broadly as their terms reasonably allow. While the term "the amino acid sequence of SEQ ID NO: 22/283" clearly indicates that the amino acid sequence contains all of SEQ ID NO: 22 or 383, the term "an amino acid sequence of SEQ ID NO: 22/383" as recited in claim 29, can be interpreted as "an amino acid sequence within SEQ ID NO: 22/383" (i.e., not all of SEQ ID NO: 22/383). Thus, in the instant case, the Examiner has broadly interpreted the term "an amino acid sequence of SEQ ID NO:22/383" to encompass a fragment of at least 2 amino acids of SEQ ID NO:22/383. In view of this interpretation, claim 29 and dependent claims 32, 81-97, 100-101, 107-111, 117-120, 126-129, 134 are directed in part to a unicellular organism comprising a first nucleic acid encoding a geranylgeranyl pyrophosphate synthase comprising at least 2 amino acids of SEQ ID NO: 22, and a second nucleic acid encoding a diterpene synthase comprising at least 2 amino acids of SEQ ID NO: 383.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

The claims require an extremely large genus of nucleic acids encoding geranylgeranyl pyrophosphate synthases and diterpene synthases. While the specification has adequately described a polynucleotide encoding the polypeptide of SEQ ID NO: 22 and a polynucleotide encoding the polypeptide of SEQ ID NO: 383, the specification fails to disclose the structures of all nucleic acids encoding any geranylgeranyl pyrophosphate synthase or diterpene synthase comprising two or more consecutive amino acids of SEQ ID NO: 22 or 383, the structural elements required in any structural homolog of the polypeptide of SEQ ID NO: 22 or 383 which are essential for enzymatic activity, or which two amino acids from SEQ ID NO: 22 or 383 are essential for enzymatic activity.

The claims require a genus of nucleic acids encoding proteins which are essentially unrelated in structure. A sufficient written description of a genus of nucleic acids may be achieved by a recitation of a representative number of species defined by their sequence or a recitation of structural features common

to members of the genus, which features constitute a substantial portion of the genus. However, in the instant case, the structural feature as interpreted, e.g., "a fragment of at least 2 amino acids of SEQ ID NO:22/383", does not constitute a substantial portion of the genus as the remainder of the structure of any nucleic acid encoding a protein comprising those structural features and having the recited activity is completely undefined and the specification does not define the remaining structural features necessary for members of the genus to be selected. In addition, there is no information as to a correlation between the structures disclosed/known in the art and the required enzymatic activity. Furthermore, while one could argue that the structures of known geranylgeranyl pyrophosphate synthases and diterpene synthases are representative of all members of the genus of enzymes encoded by the required nucleic acids, it is noted that the art teaches several examples of how even small changes in structure can lead to changes in function. See, for example, Witkowski et al. and Seffernick et al. cited previously. Therefore, since minor structural changes may result in changes affecting function, and no additional information correlating structure with the enzymatic activity required has been provided, one cannot reasonably conclude that the known structures are representative of all the enzymes encoded by the required nucleic acids.

Due to the fact that the specification only discloses a few nucleic acids encoding geranylgeranyl pyrophosphate synthases and diterpene synthases, one of skill in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention.

5. Claims 29, 32, 81-97, 100-101, 107-111, 117-120, 126-129, 134 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a unicellular organism comprising a nucleic acid encoding the polypeptide of SEQ ID NO: 22 and the polypeptide of SEQ ID NO: 383, does not reasonably provide enablement for a unicellular organism comprising a nucleic acid encoding a geranylgeranyl pyrophosphate synthase comprising a fragment of the polypeptide of SEQ ID

NO: 22 and a nucleic acid encoding a diterpene synthase comprising a fragment of the polypeptide of SEQ ID NO: 383. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2nd 1400 (Fed. Cir. 1988)) as follows: (1) quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence and absence of working examples, (4) the nature of the invention, (5) the state of prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breath of the claims. The factors which have lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed in detail below.

The breath of the claims. Claims 29, 32, 81-97, 100-101, 107-111, 117-120, 126-129, 134 are so broad as to encompass a unicellular organism comprising a nucleic acid encoding a geranylgeranyl pyrophosphate synthase comprising a fragment of the polypeptide of SEQ ID NO: 22 and a nucleic acid encoding a diterpene synthase comprising a fragment of the polypeptide of SEQ ID NO: 383. The enablement provided is not commensurate in scope with the claims due to the extremely large number of nucleic acids encoding geranylgeranyl pyrophosphate synthases and diterpene synthases required by the claimed organism for which there is essentially no structure disclosed. In the instant case, the specification enables a unicellular organism comprising a nucleic acid encoding the polypeptide of SEQ ID NO: 22 and the polypeptide of SEQ ID NO: 383.

The amount of direction or guidance presented and the existence of working examples. The specification discloses several nucleic acids encoding geranylgeranyl pyrophosphate synthases and diterpene synthases as well as unicellular organisms comprising said nucleic acids. However, the specification fails to disclose which structural elements in addition to two consecutive amino acids of

SEQ ID NO: 22 or 383 are required in a protein to have the recited enzymatic activity, and which fragments of SEQ ID NO: 22 or 383 are required in a protein to have the recited enzymatic activity.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art. The nucleotide sequence of the coding region of a polynucleotide encoding a protein determines the structural and functional properties of that protein. In the instant case, neither the specification nor the art provide a correlation between structure and activity such that one of skill in the art can envision the structure of any nucleic acid encoding a geranylgeranyl pyrophosphate synthase or diterpene synthase comprising a fragment of SEQ ID NO: 22 or 383. The art clearly teaches that structural changes in a protein to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are required for that activity is highly unpredictable. At the time of the invention there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (Introduction to Protein Structure, Garland Publishing Inc., New York, page 247, 1991) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing *de novo* stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. (Biochemistry 38:11643-11650, 1999) and Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) already discussed, where it is shown that even small amino acid changes result in enzymatic activity changes.

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification. While methods of generating or isolating variants of a nucleic acid were known in the art at the time of the invention, it was not routine in the art to screen by a trial and error process for all nucleic acids encoding geranylgeranyl pyrophosphate synthases or diterpene synthases

comprising a fragment of SEQ ID NO: 22 or 383. In the absence of some knowledge or guidance as to (1) a correlation between structure and the required enzymatic activity, and (2) the structural variability of geranylgeranyl pyrophosphate synthases and diterpene synthases and the extent of such variability, one of skill in the art would have to test an essentially infinite number of nucleic acids to determine which ones encode proteins having geranylgeranyl pyrophosphate synthase and diterpene synthase activity.

Therefore, taking into consideration the extremely broad scope of the claims, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and function, and the high degree of unpredictability of the prior art in regard to structural changes and their effect on function, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

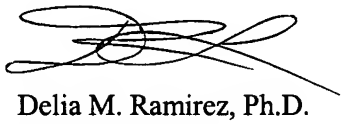
Allowable Subject Matter

6. Claims 1, 4-18, 80, 98-99, 102-106, 112-115, 122-125, 132-133 appear to be allowable over the prior art of record.

Conclusion

7. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.



Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
September 12, 2006